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Guideline on data requirements for adjuvants in vaccines for veterinary use

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The guideline replaces the Note for guidance on the use of adjuvanted veterinary vaccines (EMA/CVMP/IWP/043/97) adopted by the Committee in November 1998.

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Guideline on data requirements for adjuvants for use in veterinary vaccines

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Executive summary

The aim of the guideline is to outline the information which should be included for an adjuvant in the marketing authorisation application (MAA) dossier of veterinary vaccines as required in Section IIIb of the Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products (repealing Directive 2001/82/EC).

This guideline replaces the 'Note for Guidance on the use of adjuvanted veterinary vaccines' (EMA/CVMP/IWP/043/97).

The guideline discusses the important aspects to consider for the adjuvant/s in a veterinary vaccine and provides guidance on the information on the adjuvant, which should be included in Parts 2, 3 and 4 of the MAA. The details on the adjuvant which should be referred to in the summary of product characteristics (SPC) are also addressed.

1. Introduction (background)

An adjuvant is a substance or combination of substances which, when included in a vaccine, modulates the immune response to the vaccine active substance(s) to enhance the clinical effectiveness of the vaccine. For example, an adjuvant may increase the immunogenicity of the active substance(s) thereby reducing the amount of active substance(s) required for successful immunisation or may modify the induced protective immune response e.g. extending its duration, thereby removing the requirement for booster vaccinations or extending the interval between vaccinations. Adjuvants can also be used to optimise a desired immune response e.g. with respect to immunoglobulin classes and/or induction of cytotoxic or helper T lymphocyte responses.

Some of the mechanisms by which adjuvants may exert their activities include:

- Protection of the vaccine active substance(s) from biodegradation thus increasing their retention at the site of vaccine administration for prolonged stimulation of the immune system;
- Activation of the innate immune system by delivering signals to inflammatory cells, thus facilitating uptake of the vaccine active substance(s) and processing by antigen presenting cells (APCs);
- Distribution of the processed active substance(s) and enhancement of their presentation by APCs to the adaptive immune system to stimulate humoral and / or cell mediated immunity.

Knowledge on the modulation of the immune response obtained with one active substance - adjuvant combination cannot as a rule be extrapolated to another active substance - adjuvant combination given that adjuvant activity is a result of multiple factors and active substances vary in their physical, biological and immunogenic properties.

Adjuvants should be chosen based on the type of immune response desired and should be formulated with the active substance(s) of the vaccine in such a way that an appropriate immune response is obtained, while ensuring the safety of the dose chosen. In Section IIIb of Annex II to Regulation 2019/6 (Requirements for immunological veterinary medicinal products) references to adjuvants are made in:

IIIb.2A1. Qualitative and quantitative composition
IIIb.2C. Production and control of starting materials
IIIb.2E. Control tests on the finished product
IIIb.3F. Residue tests to be included in the pre-clinical studies

The safety and efficacy of the final formulation (active substance(s), adjuvant and excipients) should be demonstrated in accordance with safety and efficacy requirements described in Section IIIb of Annex II to Regulation (EU) 2019/6.

2. Scope

The intention of this guideline is to outline the type of data to be submitted in the MAA dossier in relation to the adjuvant(s) used in veterinary vaccines to meet the requirements of Section IIIb of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex II to Regulation (EU) 2019/6 and all other relevant EU and VICH guidelines as well as relevant European Pharmacopoeia (Ph. Eur.) monographs.

These include, but are not limited to the following:

- Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010-Rev.1);
- Substances considered as not falling within the scope of Regulation (EC) No. 470/2009 with regards to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009), often referred to as the 'out of scope list';
- Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006);
- Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012);
- VICH GL44: Target animal safety for veterinary live and inactivated vaccines;
- Ph. Eur. 0062 'Vaccines for veterinary use';
- Ph. Eur. 5.2.6 'Evaluation of safety of veterinary vaccines and immunosera';
- Ph. Eur. 5.2.7 'Evaluation of efficacy of veterinary vaccines and immunosera'.

4. Data requirements

4.1. Data requirements for Part 2 Quality (IIIb.2.)

Qualitative and quantitative composition (IIIb.2.A1.)

In the description of the qualitative and quantitative composition of the vaccine, a clear distinction should be made between adjuvant constituents and other vaccine excipients.

Where there is more than one adjuvant and / or the adjuvant(s) consists of a number of constituents, the qualitative and quantitative composition and function (e.g. immune modulator, stabiliser, emulsifier) of all of the constituents of the adjuvant(s) should be stated in the table of qualitative and quantitative particulars in the dossier. Where the adjuvant is commercially available, and a trade name is used the trade name should be included, as this is useful for pharmacovigilance purposes.

It is recognised that the details of the adjuvant composition may be considered commercially sensitive information. For commercially available and proprietary adjuvants, the adjuvant producer upon agreement with the relevant competent authority may submit any commercially confidential data required for the dossier directly to the competent authority.

It may not be necessary to disclose the exact composition of the adjuvant in publically available documents (e.g. product information and the European Public Assessment Report (EPAR)) where adequate justification is given for not providing this information and the adjuvant composition is defined in the dossier.

Product development (IIIb.2.A2.)

The chosen active substance(s) – adjuvant(s) combination, at the quantitative composition proposed for the veterinary vaccine, should be described and justified.

The following information should be provided, if available, when describing the mechanism of action of the chosen adjuvant(s) in combination with the active substance(s) in the proposed target species when the vaccine is given according to the proposed administration route(s):

- The manner in which the adjuvant(s) (and the individual constituents of the adjuvant) exerts its effects;
- The type of immune response triggered by the active substance(s) – adjuvant(s) combination;
- The type of interaction between the adjuvant(s) and the active substances(s) and the importance of the interaction to stimulate an immune response in the target species.

To support the choice of the adjuvant and of the proposed active substance(s) – adjuvant(s) combination the following points should be taken in consideration:

- An overview of the safety profile of the active substance(s) - adjuvant combination should be provided giving due consideration to the mechanism(s) of action of the adjuvant and its constituents. It is expected that the safety of the adjuvant will be addressed within the context of the target animal species and user safety assessments in Part 3 of the dossier. Where risks are identified, appropriate risk mitigation measures should be proposed in the SPC.
- Reference can be made to other marketed vaccines containing the same or similar adjuvant(s) and / or adjuvant constituents and to published literature. Reference to and reliance on publically available information may not be adequate where the concentration of the adjuvant and / or active substance(s) is higher in the new product than in veterinary vaccines authorised to date. The same applies to a combination of adjuvants used in a new vaccine being submitted for authorisation where the combined adjuvant system has not yet received an authorisation in the EU. If relevant, additional assurances or further data on the safety profile of the adjuvant system should be provided (in Part 3) in such cases.
- Reference to the vaccine efficacy studies in Part 4 of the dossier can be made to support the efficacy profile of the chosen active substance(s) – adjuvant(s) combination of the proposed target species. Data from preliminary / pilot studies generated during vaccine development can be provided in the 'Product Development' section of the dossier.

Description of the manufacturing method (IIIb.2B.)

The steps involved in the manufacturing process of the adjuvant(s) should be described if performed by the vaccine manufacturer. However, if performed by the supplier of the adjuvant an appropriate certificate of analysis (CoA) including specifications will suffice.

The steps involved in blending of the adjuvant(s) and the vaccine active substance(s) and excipients should be described in detail. Critical steps / parameters in the production and mixing processes considered important for association of the active substance(s) and the adjuvant(s) and / or adjuvant constituent(s) should be outlined (e.g. emulsification process for oil-based adjuvant, sterilisation conditions for adjuvants).

Production and control of starting materials (IIIb.2C.)

The name and a description of the adjuvant(s) and each of the adjuvant constituents where relevant (e.g. of chemical or biological origin) should be given. When of biological origin, the source of the material and a risk assessment in terms of contamination with extraneous agents and/or TSE should be provided, in line with current requirements. A certificate of analysis should be provided.

Depending on the nature of the adjuvant and its constituents, the requirements of some Ph. Eur. monographs and CVMP guidelines may also be applicable (in addition to those listed under Section 3 above). While not an exhaustive list, examples of relevant documents that may apply include:

- Ph. Eur. 2034 "Substances for pharmaceutical use";
- Ph. Eur. 5.2.5 "Management of extraneous agents in IVMPs";
- Ph. Eur. 0784 "Recombinant DNA technology, products of";
- Ph. Eur. 1483 "Products with risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products";
- Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Control tests during the manufacturing process (IIIb.2D.) and Control tests on the finished product (IIIb.2E.)

A description of the tests applied as controls for the critical steps/parameters in the production of the adjuvant(s) and /or mixing with the active substance(s) and excipients to guarantee the consistency and quality of the adjuvant in routine vaccine batches should be given as part of the overall manufacturing description in addition to tests on the finished vaccine. The limits for each test should be defined with appropriate justification and data on the validation of each test should be provided.

The choice of tests used should be justified. Items to consider include (but are not limited to):

- Suitability of the test(s) to measure the qualitative and quantitative composition of the constituents of the adjuvant(s) that have an immune-stimulating effect;
- Suitability of the test(s) to measure the physico-chemical and biological characteristics of the adjuvant(s) and / or active subtance(s) – adjuvant(s) combination to ensure the consistency and integrity of the combination in routine vaccine batches.

If available, an in vitro test should be used to test for the adjuvant(s) and / or its constituents in the finished vaccine batch. In line with the requirements of Directive 2010/63/EU and the Guideline on the principles of regulatory acceptance of 3Rs testing approaches, the continued use of in vivo tests simply on the basis that they support the performance of the active substance(s) – adjuvant(s) combination is no longer considered an adequate justification for not developing alternative in vitro tests (when alternative methods can be developed for both the adjuvant(s) and the active substance(s)).

It is recognised that there may be situations where it is difficult to quantify the adjuvant and / or its constituents in the vaccine formulation (e.g. interference with other constituents of the vaccine formulation, low concentration of the adjuvant in the formulation). In exceptional circumstances, and

only when a suitable justification can be given, alternative approaches may be acceptable, e.g. quantification of the adjuvant(s) and / or its constituents in the solution prior to addition to the active substance(s) during blending to confirm that the correct amount of adjuvant is added to the vaccine blend. However, when tests for the quantitative composition of the adjuvant(s) are not done on the finished vaccine, some level of testing should be performed to support the suitability of the association between the active substance(s) and the adjuvant(s) in the finished vaccine where possible.

Batch to batch consistency (IIIb.2F.)

Data from three consecutive finished product batches (including the proposed adjuvant), which are representative of the proposed manufacturing process should be provided in the dossier. Any deviations should be justified. Batch protocols for the consistency batches should be provided and should include results of the in-process and finished product tests proposed for the adjuvant(s) and / or its constituents.

Stability (IIIb.2G.)

During the stability studies on the vaccine, any appropriate qualitative and/or quantitative tests, preferably in vitro tests, should be performed to support the quality of the adjuvant(s) and its constituents throughout the shelf life of the vaccine.

4.2. Data requirements for Part 3 Safety (IIIb.3.)

Data should be submitted in accordance with the requirements of 'Section IIIb.3. Part 3: Safety documentation (Safety and residue tests)' of Annex II to Regulation (EU) 2019/6 and according to the requirements of Ph. Eur. 5.2.6 'Evaluation of safety of veterinary vaccines and immunosera' and VICH GL44 'Target animal safety for veterinary live and inactivated vaccines'.

Exceptionally, and where relevant, the safety parameters monitored in the vaccine target animal safety studies should be adjusted to take into consideration potential safety concerns associated with the adjuvant(s) as discussed in the Product Development section of the dossier.

For food producing animals the safety of residues of the adjuvant(s) and / or its constituents for human consumption of the foodstuffs must be addressed and an appropriate withdrawal period for the product proposed, if required.

It should be ensured that the maximum residue limit (MRL) status of each of the adjuvants and any associated constituents within a proprietary adjuvant formulation is addressed in advance of submitting the marketing authorisation dossier:

- If the adjuvant has a 'no MRL required' classification according to Regulation (EC) No 37/2010 or is included in the list of substances considered as not falling within the scope of Regulation (EC) No. 470/2009 (that is, the 'out-of-scope' list), no additional information is required.
- If the adjuvant does not have an MRL classification and is not included in the out of scope list, then the MRL status of the adjuvant must be addressed. This can be achieved by means of an MRL application or, in case of absence of pharmacological activity, by a request to include the adjuvant in the 'out of scope' list.

When assessing the user safety of the active substance(s) – adjuvant(s) combination potential hazards associated with human exposure to the adjuvant(s) should be identified in the application dossier. For example, parenterally administered vaccines containing mineral oil adjuvants represent a particular risk to the user if self-injected (Refer to "Guideline on user safety for immunological veterinary medicinal products").

Similarly, when assessing the environmental risk of the active substance(s) – adjuvant(s) combination consideration should be given to the potential harmful effects to the environment due to the adjuvant(s) or its constituents and identify any precautionary measures to reduce such risks.

4.3. Data requirements for Part 4 Efficacy (IIIb.4.)

Data should be submitted in accordance with the requirements of 'Section IIIb.4. Part 4: Efficacy documentation (pre-clinical studies and clinical trials)' of Annex II to Regulation (EU) 2019/6 and according to the requirements of Ph. Eur. 5.2.7 'Evaluation of efficacy of veterinary vaccines and immunosera'.

4.4. Data requirements for the product information

The qualitative and quantitative composition of the adjuvant(s) should be stated in Section 2 of the SPC according to the requirements of the QRD veterinary annotated product information template. It should include quantitative details of the constituent(s) responsible for the immune modulatory effect. All other constituents without such effects should be listed (only qualitative information is required).

5. Definitions

The following definitions apply to terms used in this guideline:

Active substance: The active substance is the component of the veterinary vaccine to which an immune response is desired. Vaccines may contain one or more active substances.

Adjuvant: Substance or a composition of substances which when used in a vaccine potentiates the immune response to the active substance(s) of the vaccine and / or modulates it towards a desired immune response which cannot be achieved by administration of the active substance(s) alone.

6. References

Quality Review of Documents (QRD): EMA website; veterinary product-information template;

Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin;

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) 726/2004 of the European Parliament and of the Council;

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.